REMARKS

Claims 1 and 5 have been amended by incorporating the limitations of claims 3 and 7 therein, respectively, and claims 3 and 7 have been canceled. Claim dependencies have been changed to eliminate improper multiple dependencies. No new matter has been incorporated into the claims as a result of the amendments.

Claims 1-15 have been rejected under 35 U.S.C. § 112, first paragraph, on the basis that the specification does not enable one of skill in the art to make and use the invention commensurate in scope with these claims. The claims as recited were said to be broader than the scope of enablement. The examiner noted that the claims are seen to encompass a compound in which R1 can equal all heterocyclic groups and where a method of iron chelation therapy is used to treat mammalian subjects using these compounds. The breadth of the claims also was said to encompass a method of treating iron overload disease. This rejection is traversed.

In setting forth this rejection, the examiner cited the "Wands factors," factors for determining enablement listed by the Court of Appeals for the Federal Circuit in *In re Wands*, 8 USPQ2d 1400 (1989). The first of these factors is the breadth of the claims. As noted above, claims 1 and 5 have been amended such that R1 is limited to four specific ring groups. The examiner

also had stated that the "breadth of the claims is seen to also encompass a method of treating iron overload disease." This statement is incorrect in that claim 1 is directed to a composition that is suitable for use as an *in vivo* iron chelating agent. An *in vivo* chelating agent, of course, is not equal in scope nor meaning to a method for treating iron overload disease. Presumably, the examiner intended to restrict this comment to claims 11-14, which will be addressed below.

With regard to the second Wands factor, the nature of the invention, the examiner asserted that there is no known therapeutic agent that can treat such a broad category of diseases such as iron overload disease, and also finds that the specification does not disclose how iron chelate therapy would be used to treat specific diseases. Again, Applicants remind the examiner that claims 1-10 are not directed to iron overload diseases *per se*. Furthermore, with regard to known therapeutic agents, "standard" chelators such as DFO are known therapeutic agents that are used to treat iron overload disease. Well-known experimental agents that currently are used *in vitro* in cell cultures include PIH and 311. Furthermore, papers such as Nielson et al., "Effective Treatment of Hereditary Haemochromatosis with Desferrioxamine in Selected Cases," *Br. J. Haematol.* 123(5):952 (Dec., 2003), further describe the use of

DFO as an iron chelating agent in treating disease. In addition, well-known alternate drugs to DFO, such as HBED or hydroxybenzylethylenediamine diacetic acid, have been described as removing up to 3 times more iron than DFO when tested in normal rats and in primates overloaded with iron. (See the NIH News Release of March 3, 1998 for the National Institute of Diabetes and Digestive and Kidney Diseases entitled "Researchers Identify Potential New Drug Treatment for Iron Overload, Cooley's Anemia and Sickle Cell Patients Would Benefit.") Copies of both these papers are enclosed.

Iron chelators are useful for various disease states. At present, iron chelators (such as DFO) are used for treatment of chronic iron overload disease such as β-thalassemia major. They also are useful, however, in the treatment of acute iron poisoning, such as when a young child ingests iron tablets. Experimentally, there are a wide variety of studies demonstrating that iron chelators are effective for the treatment of a number of disease states including cancer. Indeed, there now is one clinical agent, Triapine®™ (Vion Pharmaceuticals Ltd), in Phase II clinical trials, which works by binding iron to cancer cells and preventing their proliferation (iron is essential for DNA synthesis and cell cycle progression).

With regard to the disclosure in the present application, the specification clearly discloses that compounds such as DFO are well known iron chelators used for treating iron overload disease as well as other diseases, such as cancer (see page 2, line 35 - page 3, line 4; page 3, lines 13-15 and lines 23-29; and page 5, lines 19-23).

The third and fifth Wands factors are the state of the art and the level of predictability in the art. The present specification provides several specific test compounds, including PIH, 311, PCIH, PCBH, PCBBH, PXTH, PCHH and PCAH. These specific test compounds include PCIH analogues, wherein R1 is pyridine (See PCIH), substituted or unsubstituted phenyl (PCBH, PCBBH, PCAH and PCHH), and thiophene (See PCTH). With regard to an analogue wherein R1 is furan, it is submitted that a person skilled in the art would expect that this analogue would behave similarly to an analogue in which R1 is thiophene.

The fourth and sixth Wands factors are the level of ordinary skill in the art and the amount of direction provided by the inventor. With regard to these factors, the specification does provide guidance on characteristics of the composition of the invention. The examiner's attention is drawn to page 34, lines 31-36, wherein it is made clear that the strategy to design new

chelators derived from PIH was based on the advantageous properties of this compound. The compound:

(a) is effective orally

(b) has near optimal hydrophilic-lipophilic balance

(c) has high specificity and selectivity for Fe

(d) is predominantly neutral at physiological pH

(e) is economical and simple to synthesize

(f) has high chelation efficacy both *in vitro* and *in vivo*.

Each compound of the present invention preferably includes these features.

With regard to the compounds which fall within the scope of the new claims, working examples are provided to test whether compounds of the invention have the desired characteristics. Accordingly, in light of the amended claims and the examples provided in the specification, it is submitted that there is no undue burden of experimentation on the person skilled in the art to determine compounds which fall within the scope of the invention.

With regard to the final two Wands factors, the existence of working examples and the quantity of experimentation needed to make or use the invention, the specific structure of the claimed formula is provided, as is a method for making a composition of Formula 1 (See page 15, line 12 - page 16, line 8). As to the

use of the compounds as an *in vivo* iron chelator, the inventors describe experiments which test for iron uptake and iron release from pre-labeled cells (see page 18, line 11-20). Detailed experiments are described which were used to investigate the ability of an iron chelator to permeate a cell membrane and chelate intracellular iron pools (page 20, lines 26-27). It is noted that "standard" chelators, such as DFO, PIH and 311, the activity of which previously has been documented in the SK-N-MC cell line, are used as comparison compounds to the compounds of the present invention. Three of the PCIH analogues according to the present invention, namely PCTH, PCBH and PCBBH, showed activity greater than that of DFO and comparable to that of 311 and PIH. To further investigate efficacy, the efficacy of PIH, PCIH, PCTH, PCBH and PCBBH at mobilizing ^{39}Fe from SK-N-MC cells at a range of ligand concentration also was compared.

In other experiments, the effect of PCIH analogues on mitochondrial iron mobilization in reticulocytes also was tested (See page 30, line 13 - page 31, line 15). Page 30, lines 16-17 note that the inventors used "the only well-characterized model of mitochondrial Fe overload, that is reticulocytes loaded with mitochondrial non-heme ^{39}Fe."

In view of the foregoing, it respectfully is submitted that detailed experimental evidence indeed is provided in the

specification for compounds which fall within the scope of the invention.

Turning to claim 11, this claim is directed to a method of treating an iron overload disease in a subject. Iron overload diseases are well-known and well-described in the literature. A variety of iron overload diseases are described, including β-thalassemia, sideroblastic anemia, chronic liver disease secondary to alcohol, and porphyra cutanea tarda. Some iron overload disease can be associated with excessive ingestion of iron or repeated transfusion or can be inherited.

Iron overload derived from any source or disease state also can be described as hemochromatosis. Classical hemochromatosis is a defect in a molecule known as HFE, which results in an increase in iron uptake from the digestive tract leading to iron overload. The treatment for this disease involves phlebotomy (i.e., bloodletting) and iron chelation therapy is not necessary. In contrast, β-thalassemia is an iron overload disease which is induced by mutation in hemoglobin which leads to anemia. The anemia is treated using multiple blood transfusions which result in a secondary iron overload, as blood is rich in iron. All of these conditions are very well-known. Considering specific diseases, several studies have suggested that Friedreich's ataxia can be caused by an accumulation of iron in the mitochondrion.

If the disease is caused by mitochondrial iron overload, treatment regimens could include iron chelation therapy (see page 33, line 35 - page 34, line 2).

Claim 15 was rejected under 35 U.S.C. §101. This rejection has been obviated by the cancellation of claim 15.

All of the pending claims have been rejected under 35 U.S.C. §102(b) as anticipated by Schurter et al. on the basis that the reference discloses claimed compound 1,2,3-benzothiadiazole-7-carboxylic acid. Applicants respectfully submit that this reference does not disclose compounds which fall within the scope of claim 1, i.e., of falling within the scope of Formula 1. The benzothiadiazole compound specifically noted by the examiner does not fall within the scope of the claims. Furthermore, on review of the document as a whole, it is submitted that none of the compounds disclosed in this reference fall within the scope of claim 1. Finally, it is noted that the reference is directed to a process and a composition for immunizing plants against disease. It does not disclose or suggest a compound suitable for use *in vivo*, nor does it disclose an iron chelating agent.

Claims 1-7 and 9 also have been rejected under 35 U.S.C. §102(b) as anticipated by Schwamborn et al. on the basis that it discloses claimed compound 1-pyrrolidinecarbothioic acid, (2-pyridinylmethylene)hydrazide. This rejection also is traversed.

The English abstract for this reference discloses that for Formula (I), R3 is C(X)-R4, wherein X can be O and R4 is SR5, NHR5, NR6R5, OR5 or NHNHR5. Accordingly, R4 is not a heterocyclic or aromatic ring *per se*, but instead must include a linking group selected from S, N or O. Accordingly, the disclosed compound does not fall within the scope of the presently claimed compounds.

Applicants respectfully submit that the claims now pending in this application are in condition for allowance.

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